The diagnosis and treatment of von Willebrand disease in children

Robert J Klaassen MD FRCPC, Jacqueline M Halton MD FRCPC

RJ Klaassen, JM Halton. The diagnosis and treatment of von Willebrand disease in children. Paediatr Child Health 2002;7(4):245-249.

von Willebrand disease is the most common bleeding disorder seen in children and it affects approximately 1% of the population. Because the bleeding symptoms in von Willebrand disease are generally mild, the diagnosis is often delayed. Prompt diagnosis and management can help to avoid potentially life-threatening bleeding events and unnecessary exposure to blood products. In this review, the various types of von Willebrand disease are outlined, the difficulties in diagnosis are discussed and the therapeutic approach to this common disorder is described.

Key Words: *Child; Factor VIII; von Willebrand disease; von Willebrand factor*

Le diagnostic et le traitement de la maladie de von Willebrand chez les enfants

La maladie de von Willebrand est le trouble hémorragique le plus courant chez les enfants. Elle touche environ 1 % de la population. Puisque les symptômes hémorragiques de cette maladie sont généralement bénins, le diagnostic est souvent tardif. Un diagnostic et une prise en charge rapides peuvent toutefois contribuer à éviter des hémorragies pouvant mettre la vie en danger et une exposition inutile aux produits sanguins. Dans la présente analyse bibliographique, les divers types de maladie de von Willebrand sont soulignés, les difficultés reliées au diagnostic sont abordées, et la méthode thérapeutique de ce trouble courant est décrite.

Paediatricians are frequently asked to assess children with easy bruising and epistaxis, or adolescents with heavy menstrual periods. Because the bleeding tendency is generally mild, a diagnosis of von Willebrand disease (VWD) is often delayed. Eric von Willebrand (1) first described VWD in 1926 when he reported an autosomal dominant bleeding disorder in a family living on the Åland Islands off the coast of Finland. VWD is now recognized as a heterogeneous disorder of hemostasis caused by quantitative or qualitative abnormalities of the protein von Willebrand factor (VWF). The deficiency in this protein results in mucocutaneous bleeding, and post-traumatic or postsurgical bleeding. Diagnosing VWD may be problematic because of fluctuating clotting factor levels. The pathophysiology, laboratory diagnosis, and treatment of children and adolescents with VWD are discussed.

EPIDEMIOLOGY

VWD is estimated to occur in 1% of the general population. Two paediatric studies, one involving the screening of 1218 healthy Italian children and another involving 600 American children, found 10 (0.82%) Italian and eight (1.3%) American children with VWD. It is important to note that all affected children had at least one significant bleeding symptom and a family member with bleeding symptoms, in addition to fulfilling the laboratory criteria.

Department of Pediatrics, Division of Hematology/Oncology, Children's Hospital of Eastern Ontario, Ottawa, Ontario
Correspondence and reprints: Dr Jacqueline Halton, Division of Hematology/Oncology, Department of Paediatrics, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario K1H 8L1. Telephone 613-737-2370, fax 613-738-4828, e-mail halton@cheo.on.ca

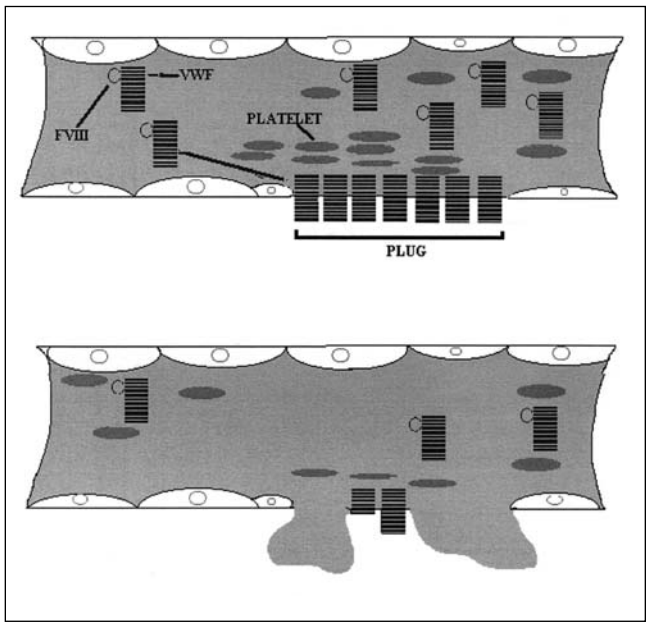

Figure 1) Top *Normal von Willebrand factor (VWF) function in adhesion of platelets and binding of Factor VIII (FVIII).* **Bottom** *Vessel damage as a result of Von Willebrand's disease (adapted with permission from reference 21)*

The prevalence of VWD was the same in all ethnic groups that were studied (2,3).

PATHOPHYSIOLOGY

VWD is caused by either decreased quantity or abnormal function of a large multimeric protein, VWF. The protein ranges in size from 450 kDa to over 10,000 kDa and is located at chromosome 12p13.2. VWF is made in the endothelium and by megakaryocytes. This protein has two roles: the binding of platelets to exposed collagen at sites of vascular injury, and the binding and stabilization of factor VIII (Figure 1) (4).

VWD has recently been classified into types 1, 2 and 3 (Table 1). Type 1 VWD is caused by low levels of functionally normal protein (10% to 50% of normal values) and accounts for approximately 80% of all cases of VWD. Type 2 is seen in 15% to 20% of patients with VWD and is caused by variable amounts of functionally abnormal VWF. Type 2 is further subdivided into type 2A, in which the larger protein multimers are missing; type 2B, in which VWF has increased affinity for platelets; type 2M, in which there is a normal protein multimer pattern; and type 2N, in which the protein has markedly decreased affinity for factor VIII. Type 3 occurs in less than 1% of VWD cases and is the result of the virtual absence of VWF (5).

GENETICS

Type 1 VWD is typically transmitted in an autosomal dominant manner. The genetic mutations seen include nonsense mutations, deletions and frameshifts. Type 2 occurs primarily as an autosomal dominant disorder, but may also show recessive inheritance. The primarily missense mutations seen in type 2 VWD occur within the various functional domains of the *VWF* gene, resulting in the four clinical phenotypes (types 2A, B, M and N). Type 3 VWD occurs in patients who are either homozygous or compound heterozygous for the type 1 mutations (4).

DIAGNOSIS

Patients with VWD typically present with mucocutaneous bleeding, most commonly bruising with minimal or no apparent trauma, recurrent spontaneous epistaxis and oral cavity bleeding events. Other bleeding symptoms include prolonged bleeding following skin laceration or oral surgery, and spontaneous gastrointestinal bleeding (6). Thirteen per cent of women presenting with menorrhagia have VWD (7).

Diagnosing VWD can be problematic. A definite diagnosis requires a significant bleeding history, a family history of bleeding and abnormal laboratory findings. Patients with abnormal laboratory findings, combined with either a personal or a family history of bleeding should be labelled as having probable VWD, although the distinction between definitive and probable VWD does not alter the clinical management of the disease.

TABLE 1
Laboratory results according to type of von Willebrand's disease

Type	Defect	Laboratory abnormality VWF:Ag	VWF:Rco	Multimers	RIPA	RIPA-LD	Factor VIII
1	Quantitative	↓	↓	↓*	↓ or normal	Absent	↓ or normal
2A	Qualitative	↓ or normal	↓↓	↓ HMW	↓↓	Absent	↓ or normal
2B	Qualitative	↓ or normal	↓	↓ HMW	normal	↑	↓ or normal
	↑ affinity for platelets						
2M	Qualitative	↓ or normal	↓↓	normal	↓	Absent	↓ or normal
2N	Qualitative	↓ or normal	↓ or normal	normal	↓ or normal	Absent	↓↓
	↓ affinity for factor VIII						
3	Quantitative	↓↓↓	↓↓↓	↓↓↓	↓↓↓	Absent	↓↓↓

**Uniform decrease in multimer pattern. ↑ Increased; ↓ Decreased. HMW High molecular weight multimers; LD Low dose; RIPA Ristocetin-induced platelet aggregation; VWF:Ag von Willebrand factor antigen; VWF:CBA von Willebrand factor collagen binding assay; VWF:Rco von Willebrand factor ristocetin cofactor. Adapted with permission from reference 22*

SCREENING TESTS

Unfortunately, there are no reliable screening tests available for VWD. Commonly used tests include the activated partial thromboplastin time (PTT), bleeding time (BT) and, more recently, the platelet function analyzer (PFA-100 [Dade Behring Inc, USA]). The PTT may be abnormal if the level of factor VIII is sufficiently decreased in conjunction with a low quantity of VWF, but a normal PTT does not exclude VWD. The BT can be prolonged in severe VWD, but has very poor sensitivity; one study of 26 children with definite type 1 VWD found only seven patients with prolonged BT (27%) (6). The PFA-100 closure times are much more reproducible than those of BTs and have greater than 90% sensitivity and specificity for VWD (6). Most Canadian laboratories do not carry the PFA-100 machine, but it is mentioned here because it may become more widely used. Due to the various problems with screening tests, any patient with symptoms suggestive of VWD or a family history of VWD should immediately have VWF antigen (VWF:Ag) and VWF ristocetin cofactor (VWF:Rco) testing done. This testing is explained more fully in the section on laboratory diagnosis. Multimeric analysis can be done when the diagnosis is confirmed, and when there is a discrepancy between the VWF:Ag and VWF:Rco. A normal BT and PTT do not rule out VWD.

LABORATORY DIAGNOSIS

The laboratory diagnosis of VWD depends on the measurement of both the amount and activity of VWF (Table 1). The VWF:Ag assay is a measure of the quantity of the factor. VWF function is determined in most laboratories by measuring the VWF:Rco by using a platelet aggregometer or by ELISA. Ristocetin is an antibiotic that promotes the binding of VWF to platelets. A newer method for assessing the activity of VWF is the VWF collagen binding assay. Unfortunately, both measures of VWF function are subject to considerable technical problems, with high relative interassay variability and high interlaboratory variability (8). Adding to the difficulty of making a diagnosis, VWF levels can increase in response to a variety of stressors and in certain chronic illnesses. It is, therefore, important to repeat tests to confirm or rule out VWD.

When interpreting laboratory results, the fact that the amount and activity of VWF varies according to blood type should be considered. People with blood group O have significantly lower levels of both VWF:Ag and VWF:Rco than people with non-O blood type. However, there is controversy as to whether the normal ranges should be adjusted according to blood group. A recent British study found similar bleeding symptoms in patients with mildly decreased VWF independent of blood type (9).

Other useful tests include factor VIII coagulation activity (FVIII:C), VWF multimer levels and ristocetin-induced platelet aggregation. Factor VIII is dependent on VWF for stabilization in the circulation and, therefore, the quantity is reduced when the VWF:Ag level is below normal. In type 3 VWD, the FVIII:C levels are usually less than 10% of normal, and the patient can present with symptoms similar to those of a moderate hemophiliac. In type 2N VWD, in which VWF has decreased affinity for factor VIII, a low FVIII:C level may be the only detectable abnormality and, therefore, the VWD can easily be misdiagnosed as hemophilia A. VWF factor VIII collagen binding assay or DNA sequencing of the binding region of VWF to factor VIII is required to confirm the diagnosis.

VWF multimer analysis provides the multimeric pattern of the VWF and is essential for determining the type of VWD. There is a uniform decrease in the multimer pattern in type 1 VWD, whereas there is a selective loss of high molecular weight multimers in types 2A and 2B. Ristocetin-induced platelet aggregation (RIPA) is used primarily to distinguish type 2A from type 2B. RIPA is virtually absent in type 2A, but platelet aggregation occurs even at low concentrations of ristocetin in type 2B (4).

TABLE 2
List of medications with antiplatelet effects

Antiplatelet agents
Acetylsalicylic acid
Nonsteroidal anti-inflammatory agents
Dipyridamole
Ticlopidine
Antimicrobial agents
High dose penicillins
Cephalosporins
Nitrofurantoin
Hydroxychloroquine
Cardiovascular medications
Propanolol
Furosemide
Calcium channel blockers
Quinidine
Others
Antihistamines
Caffeine
Valproate
Heparin
Tricyclic antidepressants
Phenothiazines
Ethanol

Data from reference 19

TREATMENT

Once the diagnosis is established, the treatment approach has two main components: patient education and selection of the appropriate therapy. Physician must instruct patients to avoid medications with antiplatelet activity by checking the ingredients in prescription and over-the-counter prepa-

TABLE 3
Summary of management of von Willebrand disease (VWD)

Type of VWD	Type of bleeding	Treatment* DDAVP	Treatment* Humate-P (VWF:Rco†)
Type 1 and 2A			
mild (VWF:Ag >30%)	minor‡	DDAVP (0.3 μg/kg) (DDAVP responder)	
moderate (VWF:Ag <30%)	minor	DDAVP (0.3 μg/kg) (DDAVP responder)	
		DDAVP nonresponder	40–50 IU/kg, 1 to 2 doses (rarely required)
	major§		50–70 IU/kg loading dose, then 40–60 IU/kg, every 8 to 12 h for 3 days, then 40–60 IU/kg daily up to 7 days
Types 2B and 3	minor		40–50 IU/kg, 1 to 2 doses
	major		60–80 IU/kg loading dose, then 40–60 IU/kg, every 8 to 12 h for 3 days, then 40–60 IU/kg daily up to 7 days

**Antifibrinolytics should be added when treating mucosal bleeding; †Dosage (IU VWF:Rco/kg body weight) (20); ‡Examples of minor bleeding include: epistaxis, oral bleeding, menorrhagia; §Examples of major bleeding include: intracranial hemorrhage, gastrointestinal bleeding, traumatic hemorrhage. VWF:Ag von Willebrand factor antigen; VWF:Rco von Willebrand Factor ristocetin cofactor. Desmopressin acetate (DDAVP Ferring Inc, Canada)*

rations for acetylsalicylic acid-containing medications (Table 2). It is essential that patients understand the importance of coordinating the medical management of bleeding episodes and the implementation of prophylaxis before surgical procedures. A referral to a comprehensive hemophilia care centre for follow-up care is recommended.

The choice of treatment for patients with VWD depends on the clinical severity, the type of VWD and the risk of bleeding. The three main therapeutic modalities used in the treatment of VWD are desmopressin acetate (DDAVP Ferring Inc, Canada), transfusion with plasma concentrates that contain VWF and antifibrinolytic agents.

Desmopressin acetate

In the majority of minor bleeding episodes, DDAVP and antifibrinolytic agents usually suffice. DDAVP is a synthetic analogue of the antidiuretic hormone, vasopressin. In 1977, Mannucci et al (10) first described the use of DDAVP to control bleeding in patients with VWD. DDAVP has been since used in VWD patients with mild to moderate bleeding problems and for the prophylaxis of patients undergoing surgical procedures (Table 3). DDAVP is the preferred treatment of choice in types 1 and 2A VWD because it is a synthetic product (10,11) and, therefore, carries no risk of transmitting bloodborne viral infections.

The mechanism by which DDAVP aids hemostasis is by increasing plasma levels of factor VIII:C and VWF through their release from endothelial storage sites (12). Following intravenous administration of DDAVP at a dose of 0.3 μg/kg, plasma levels of FVIII:C transiently increase three- to sixfold above basal levels, the bleeding time shortens, and the plasma FVIII:C and VWF levels increase within 15 to 30 min, peak within the first hour, then decline over 4 to 8 h (13). DDAVP is also effective when administered subcutaneously. A patient's response to DDAVP is reproducible and should be determined soon after diagnosis of VWD, before a bleeding complication or surgery.

A concentrated intranasal spray preparation of desmopressin acetate (Octostim, Ferring Inc, Canada), is equally effective in patients with type 1 VWD and permits the home treatment of mild bleeding episodes. In children older than five years of age, a single spray (150 μg) in one nostril is effective, while in adults, one spray into each nostril is effective. The intranasal DDAVP spray used to treat diabetes insipidus is too dilute to elicit a hematological response (10 μg per spray), so it is imperative that the correct preparation be used.

When patients with VWD receive DDAVP at closely spaced intervals, some may become less responsive (14). After a second dose of DDAVP, Mannucci et al (15) found a 30% reduction of the FVIII:C response. The development of tachyphylaxis in patients receiving multiple doses of DDAVP at close intervals is due to the depletion of factor VIII and VWF in the storage pool sites (12).

The side effects of DDAVP are usually benign and include facial flushing, headache, mild tachycardia, nausea and abdominal cramps. Water retention, hyponatremia and seizures have been reported in young children and infants who received multiple doses of DDAVP and aggressive hydration (16). Guidelines for the use of DDAVP in young children have been reported by Smith et al (17) and include baseline electrolytes and serum osmolality, fluid restriction to 75% maintenance, close monitoring of serum sodium and urine output for 24 h, and restriction of repeat doses of DDAVP if possible (17).

DDAVP is contraindicated in patients with Type 2B or 3 VWD. Type 2B patients may develop in vivo platelet aggregates and thrombocytopenia (18). Type 3 patients are usually unresponsive to DDAVP.

Plasma concentrates

Transfusions with plasma products containing VWF are reserved for patients who are unresponsive to DDAVP or for patients with type 2 or 3 VWD for treatment of bleeding episodes and for surgical procedures. This group of patients should be immunized against hepatitis B in anticipation of future use of factor concentrates. Concentrates that contain VWF include cryoprecipitate and intermediate-purity factor VIII concentrates. Cryoprecipitate is no longer recommended for use in the treatment of VWD due to the risk of bloodborne viruses. Recombinant factor VIII products and ultra-purity factor VIII concentrates do not contain sufficient quantities of VWF and are, therefore, not effective treatments. The concentrate currently available in North America with the highest concentration of VWF is Humate-P. The plasma product is made from pooled plasma pasteurized to inactivate bloodborne viruses. The manufacturer's package inserts identify the VWF:Rco activity expressed in international units. One international unit corresponds to the level of VWF:Rco found in 1 mL of fresh-pooled human plasma. An infusion of 1 IU/kg of VWF:Rco raises the plasma level of VWF:Rco by 1.5 IU/dL. The recommendations for the treatment of VWD are presented in Table 3.

Antifibrinolytics

For bleeding or surgery in the oral cavity, an antifibrinolytic agent should be used. Tranexamic acid (Cyclokapron, Pharmacia & Upjohn, Canada) is an antifibrinolytic agent that can be used along with DDAVP or factor concentrates for dental surgery or mouth bleeding events. A dose of 25 mg/kg orally, every 8 h for 10 days, is required to prevent fibrinolysis and allow wound healing. A 5% solution of tranexamic acid mouthwash made from the intravenous preparation can effectively prevent local bleeding in minor oral cavity bleeding.

Aminocaproic acid (Amicar, Wyeth-Ayerst, Canada) is another antifibrinolytic agent currently in use. The dose is 50 to 100 mg/kg every 4 to 6 h for seven to 10 days (maximum 24 g/24 h). Generally, antifibrinolytic agents are not recommended for internal hemorrhages.

CONCLUSIONS

VWD is a heterogeneous disorder caused by abnormalities of the VWF. It is imperative that family doctors and paediatricians become familiar with the treatments for VWD and the interpretation of laboratory investigations to evaluate the young child and adolescent with VWD. Most importantly, patients need to be educated about the disease to coordinate treatment and prevent complications.

ACKNOWLEDGEMENTS: The authors thank Melissa Johnson and Margaret Humphreys for their help in preparing the manuscript.

REFERENCES

1. Von Willebrand E. Hereditary pseudohemofili. Finnish Lakarsallskapets Handl 1926;67:7-112.
2. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood 1987;69:454-9.
3. Werner EJ, Broxson EH, Tucker EL, et al. Prevalence of von Willebrand disease in children: A multiethnic study. J Pediatr 1993;123:893-8.
4. Sadler JE, Mannucci PM, Berntorp E, et al. Impact, diagnosis and treatment of von Willebrand disease. Thromb Haemost 2000;84:160-74.
5. Sadler JE, Matsushita T, Dong Z, Tuley EA, Westfield LA. Molecular mechanism and classification of von Willebrand disease. Thromb Haemost 1995;74:161-6.
6. Dean JA, Blanchette VS, Carcao MD, et al. von Willebrand disease in a pediatric-based population – Comparison of type 1 diagnostic criteria and use of PFA-100® and a von Willebrand factor/collagen-binding assay. Thromb Haemost 2000;84:401-9.
7. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. Lancet 1998;351:485-9.
8. Favaloro EJ, Koutts J. Laboratory assays for von Willebrand factor: Relative contribution to the diagnosis of von Willebrand's disease. Pathology 1997;29:385-91.
9. Nitu-Whalley IC, Lee CA, Griffioen A, Jenkins PV, Pasi KJ. Type 1 von Willebrand disease – A clinical retrospective study of the diagnosis, the influence of the ABO blood group and the role of the bleeding history. Br J Haematol 2000;108:259-64.
10. Mannucci PM, Ruggeri ZM, Pareti FI, Capitanio A. 1-desamino-8-D-arginine vasopressin: A new pharmacological approach to the management of haemophilia and von Willebrands' diseases. Lancet 1977;i:869-72.
11. Mannucci PM, Ruggeri ZM, Pareti FI, Capitanio A. DDAVP in haemophilia. Lancet 1977;ii:1171-2.
12. Takeuchi M, Nagura H, Kaneda T. DDAVP® and epinephrine-induced changes in the localization of von Willebrand factor antigen in endothelial cells of human oral mucosa. Blood 1988;72:850-4.
13. Schneppenheim R, Thomas KB, Sutor AH. Von Willebrand disease in childhood. Semin Thromb Hemost 1995;21:261-75.
14. Lowe G, Pettigrew A, Middleton S, Forbes CD, Prentice CR. D.D.A.V.P. in haemophilia. Lancet 1977;ii:614-5.
15. Mannucci PM, Bettega D, Cattaneo M. Patterns of development of tachyphylaxis in patients with haemophilia and von Willebrand disease after repeated doses of desmopressin (DDAVP®). Br J Haematol 1992;82:87-93.
16. Shepherd LL, Hutchinson RJ, Worden EK, Koopmann CF, Coran A. Hyponatremia and seizures after intravenous administration of desmopressin acetate for surgical hemostasis. J Pediatr 1989;114:470-2.
17. Smith TJ, Gill JC, Ambruso DR, Hathaway WE. Hyponatremia and seizures in young children given DDAVP®. Am J Hematol 1989;31:199-202.
18. Holmberg L, Nilsson IM, Borge L, Gunnarsson M, Sjorin E. Platelet aggregation induced by 1-desamino-8-D-arginine vasopressin (DDAVP) in Type IIB von Willebrand's disease. N Engl J Med 1983;309:816-21.
19. Werner EJ. von Willebrand disease in children and adolescents. Pediatr Clin North Am 1996;43:683-707.
20. Scott JP, Montgomery RR. Therapy of von Willebrand disease. Semin Thromb Hemost 1993;19:37-47.
21. What is von Willebrand disease? King of Prussia: Aventis Behring. <www.allaboutbleeding.com>. (Version current at April 3, 2002).
22. Montgomery RR, Scott JP. Hemostatis: Disease of the fluid phase. In: Nathan D, OskiF, eds. Haematology of Infancy and Childhood, 4th edn. Philadelphia: WB Saunders, 1993:1605-50.